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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/763,462	05/01/2001	Jehad Charo	1430-264	7394

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EXAMINER	
QIAN, CELINE X	

ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 02/13/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/763,462	CHARO ET AL.	
	Examiner	Art Unit	
	Celine X Qian	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *9/11/03,11/25/03*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-26* is/are pending in the application.

4a) Of the above claim(s) *14-23* is/are withdrawn from consideration.

5)☒ Claim(s) *25 and 26* is/are allowed.

6)☒ Claim(s) *1-13 and 24* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *23 February 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-26 are pending in the application. Claims 14-23 are withdrawn from consideration for being directed to non-elected subject matter. Claims 1-13, 24-26 are currently under examination.

This Office Action is in response to the Amendment filed on 9/11/03 and 11/25/03.

Response to Amendment

The rejection of claims 1-13 and 24-26 under 35 U.S.C.103 (a) is maintained for reasons discussed in the office action mailed on and further discussed below.

Response to Arguments

Election/Restrictions

Applicants argue that the special technical feature shared by the compounds recited by claim 1 is that they are all Schiff base forming compound. Applicants assert that the compounds can be patentably distinct from each other and still share a special technical feature, which are directed to a single general inventive concept. Applicants also state that they did not regard each compound as a distinct invention because whether or not the compounds are distinct is not relevant to conclude that they share a special technical feature. Applicants further indicate that claim 25 and 26 are directed to the elected invention. Lastly, Applicants argue that examination of claims 14-23 are requested in view of the examination of the product claim 24.

These arguments are fully considered. In response to Applicant's argument regarding special technical feature, Applicants are reminded that the recited compounds are all Schiff base forming compound is not considered a special technical feature because they do not make a contribution over the prior art (see disclosure of US5,508,310). According to PCT rule 13.2, the

expression of "special technical feature" means those technical features that define a contribution that each of the invention, considered as a whole, makes over prior art (see MPEP Annex B). It is unclear how Applicants reach the conclusion that these compounds share a special technical feature and are distinct from each other. However, for the record, Applicants state that they do not regard each compound as a distinct invention.

Claims 25 and 26 are currently under examination for being directed to elected invention. However, claims 14-23 will not be examined for reasons set forth of the record mailed on 10/9/01 and 1/16/02. This requirement has already been made final in the office action mailed on 1/16/02. Should Applicants traverse this requirement, Applicant may file a petition under 37 CFR 1.144 (see MPEP 818.03 (c)).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-9, 11-13 and 24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Rhodes et al., in view of Herrman et al.

Claim 10 is rejected under 35 U.S.C. 103 (a) as being unpatentable over Rhodes et al., in view of Herrman et al. and Bellhouse et al.

In response to this rejection, Applicants argue that the claimed invention is not obvious because neither motivation nor reasonable expectation of success is shown by the evidence of

record, wherein the different mechanisms and objectives of protein vaccines and DNA vaccines do not support the use of Schiff base compound as an adjuvant for DNA vaccines based on its use of an adjuvant for protein vaccines. Applicants assert that there were good reasons to have believed that tucaresol would not work in the setting of a DNA vaccine, hence, there is no expectation of success. Applicants state that the immune responses elicited by protein vaccine (both viral and non-viral micro-organisms) utilizes mechanism illustrated by either pathway A or B (attached figure), whereas immune responses elicited by DNA vaccine utilize a unique mechanism of antigen handling that involves neither A or B. Applicants regard the major difference between the two is that the wild type infection involves an array of danger signals and co-stimulatory signals initiated by pathogen associated molecular patterns during the uptake/entry phase to APC which is not presented in DNA vaccine. Applicants assert that adjuvants and tucaresol work on co-stimulatory mechanisms and do not affect the recognition of antigen by the T cell receptor or the signal it transduces. Applicants further assert that the co-stimulatory environment associated with DNA vaccination is absent or very weak compare to the one associate with conventional protein vaccine, hence tucaresol is only effective in pathway A and B, but not in DNA vaccine. Applicants also indicate the surprising feature of the invention is the demonstration of a TH2 response instead of TH1 response as reported earlier. Applicants reiterate their comments that known immuno-potentiating agents have been tried with DNA vaccination with limited success, whereas conventional adjuvants such as alum are not effective with DNA vaccination. Applicants further argue that Herrman et al. do not disclose particular adjuvants which might expect to work in DNA vaccination. Applicants ask the Examiner to provide evidence for the statement that "signal 1 is considered the same for natural infection,

conventional vaccines and DNA vaccines," and "protein antigens can be secreted by transfected cells and then taken up by antigen presenting cells." Therefore, Applicants conclude that the combination of Rhode and Herrman references do not suggest a reasonable expectation of success to use tucaresol as adjuvant in DNA vaccination.

Applicants' argument has been fully considered but deemed not persuasive. The Examiner acknowledges that not every known immuno-potentiating agents that functions in protein vaccination would be effective in DNA vaccination, however, there is sufficient teaching to support that there is a reasonable expectation of success that tucaresol would potentiate immune response with DNA vaccination. As discussed previously, Rhodes et al. teach that the mechanism by which the Schiff base-forming compounds (including tucaresol) influence immune responses is by reacting with amino groups on the surface of lymphocytes and antigen presenting cells, thereby provide co-stimulation to T-cells, amplifying the co-stimulation provided by physiological Schiff base-formation between ligands on the surface of cells (see col.16, lines 49-56). In addition, reference 10 cited by Applicants (Rhodes et al 1995) teaches that convergence of Schiff base signaling with TCR signaling has been identified at the level of tyrosyl phosphorylation of the MAP-kinase ERK2 (see page 73, bottom of 1st col. through top of 2nd col). Therefore, tucaresol provide immuno-potentiating response by direct engaging T cells and providing signals that converges with signal 1 result from TCR-antigen ligation. This signal 1 is considered same for natural infection, conventional vaccines and DNA vaccines (see Figure D, legend). This statement is in the legend of Figure D provided by Applicants.

Applicants assert that Figure C represents the delivery of antigen as DNA that differs from pathway A and B in which the antigen is taken up either by viral receptor or endocytosis.

However, protein antigen encoded by DNA can also be secreted from the cell (the claims have no limitation on what cell type the DNA is introduced) and subsequently taken up by antigen presenting cells, and produce a MHC class II response which resembles the pathway illustrated in Figure B. The level of skill in the relevant art is high. Producing nucleic acid sequence encoding an antigen with a secretory signal is routinely done. Therefore, by forming Schiff base directly with CD4+ T cell, thus amplifying co-stimulatory effects provided by physiological Schiff base formation between ligands on the surface of the cells, there is reasonable expectation that tucaresol would enhance immune response elicited by the antigen.

The Examiner acknowledges that Applicants have demonstrated that co-administration of tucaresol and DNA encoding HSP-65 elicits TH2 mediated antibody response in addition to previously reported TH1 response. However, this finding is not a limitation in the presently claimed invention.

It would have been obvious to use Schiff base forming compound such as tucaresol to enhance immune response to DNA vaccination because of the combination teaching of Rhodes et al and Herrman et al. as discussed in the two previous office action. Rhodes et al. has demonstrated that tucaresol increased T-lymphocyte priming to antigen and increased antibody production (see Figure 1-7). Rhodes et al. teach that these compounds can be used as a vaccine adjuvant (see col. 9, lines 38-40). This notion is also reiterated in reference 10 cited by Applicants (Rhodes 1995, page 73, top left). Therefore, Applicants does not provide sufficient evidence that tucaresol would not function as a vaccine adjuvant in the setting of DNA vaccination. Rather, Applicants assert that co-stimulatory environment is absent or weak in the case of DNA vaccine. This should provide additional motivation for one of ordinary skill of art

to use Schiff base forming compound to potentiate immune response because this class of compound specifically enhance co-stimulatory effect. As such, the claimed invention would have been *prima facie* obvious to one of ordinary skill of art at the time the invention was made.

Interview

During the interview conducted on 11/24/03, Dr. Rhodes discussed the non-obviousness of the invention over the prior art. It is agreed that this information will be submitted in the form of a declaration to overcome the 103 (a) rejection of the record. However, the declaration has not been received prior to the preparation of this office action. Therefore, this rejection is maintained. Should the declaration be received prior to the mailing date of the action, it will be considered.

Conclusion

Claims 25 and 26 are allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

This application contains claims 14-23 drawn to an invention nonelected with traverse in the response filed on 12/3/2001. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period

will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Celine X Qian whose telephone number is 703-306-0283. The examiner can normally be reached on 9:00-5:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel Ph.D. can be reached on 703-305-1998. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Celine Qian, Ph.D.

Anne-marie Falk

ANNE-MARIE FALK, PH.D
PRIMARY EXAMINER